PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 6709-WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06682	International filing date *(day/month/year)* 25.06.2003	Priority date *(day/month/year)* 27.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K38/17		
Applicant UNIVERSITY OF ZURICH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.12.2003	30.09.2004
Name and mailing address of the international preliminary examining authority European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx. 523656 epmu d Fax +49 89 2399 - 4465	Authorized Officer Böhmerova, E Telephone No +49 89 2399-7859

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06682

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-44 as originally filed

Claims, Numbers

1-14 as originally filed

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 8-14

   because:

   ☒ the said international application, or the said claims Nos. 8-14 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,6,8,13
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1,6,8,13
Industrial applicability (IA)	Yes:	Claims	1,6
	No:	Claims	-

2. Citations and explanations

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06682

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Independent claims 8 , 13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited documents

Reference is made to the following documents:

D1: DINARELLO C A ET AL: 'Blocking IL-1: interleukin 1 receptor antagonist in vivo and in vitro.' IMMUNOLOGY TODAY, vol. 12, no. 11, November 1991, pages 404-410

D2: MANDRUP-POULSEN THOMAS ET AL: 'Involvement of interleukin 1 and interleukin 1 antagonist in pancreatic beta-cell destruction- in insulin-dependent diabetes mellitus.' CYTOKINE, vol. 5, no. 3, 1993, pages 185-191

D3: MEIER CHRISTOPH A ET AL: 'IL-1 receptor antagonist serum levels are increased in human obesity: A possible link to the resistance to leptin?' JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 87, no. 3, March 2002, pages 1184-1188

D4: DONATH MARC Y ET AL: 'Hyperglycemia-induced beta-cell apoptosis in pancreatic islets of Psammomys obesus during development of diabetes.' DIABETES, vol. 48, no. 4, April 1999, pages 738-744

D5: EP-A-1 018 514 (SUNTORY LTD) 12 July 2000

D6: BEDOYA F J ET AL: 'PYRROLIDINE DITHIOCARBAMATE PREVENTS IL-1-INDUCED NITRIC OXIDE SYNTHASE MRNA, BUT NOT SUPEROXIDE DISMUTASE MRNA, IN INSULIN PRODUCING CELLS', BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 210, no. 3, 25 May 1995, pages 816-822

D7: YAMAMOTO YUMI ET AL: 'Role of the NF-kappaB pathway in the pathogenesis of human disease states' CURRENT MOLECULAR MEDICINE, vol. 1, no. 3, July

2001, pages 287-296

D8: FLODSTROEM M ET AL: 'CYTOKINES ACTIVATE THE NUCLEAR FACTOR KAPPAB (NF-KAPPAB) AND INDUCENITRIC OXIDE PRODUCTION IN HUMAN PANCREATIC ISLETS' FEBS LETTERS, vol. 385, no. 1/2, 1996, pages 4-6

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

Novelty

The subject-matter of independent claims 1,6, 8,13 is considered to be novel under Art. 33(1) and (2) PCT for the following reasons:

Present claims are directed to the use of interleukin 1 receptor antagonist (IL-1Ra) or pyrrolidinedithiocarbamate (PDTC) for the preparation of a medicament for the treatment or prophylaxis of type II diabetes. None of the cited documents teach such activity of IL-1Ra or PDTC.

Both D1 and D2 teach that IL-1 is an effector of immune-mediated destruction of beta cells and that the administration of IL-1Ra to rat significantly delays the onset of insulin dependent spontaneous diabetes (type I diabetes). None of D1 or D2 teaches the use of IL-1Ra in the treatment of type II diabetes.

D3 teaches that leptin is capable of inducing expression and secretion of IL-1Ra from human monocytes. D3 does not mention any connection between IL-1Ra levels and diabetes type II.

D4 teaches that exposure of islets from diabetes-prone Psammomys obesus to high glucose levels resulted in a dose dependent increase in beta cell DNA fragmentation and that hyperglycemia induced beta cell death may contribute to the evolution of type II diabetes. However, D4 fails to mention any role of IL-1Ra or PDTC in preventing this mechanism.

D5 teaches the use of NF-kappaB inhibitors for the treatment of diseases caused by the activation of NF-kappaB including diabetes type II. D5 does not mention the use PDTC or IL-1Ra.

D6 teaches that PDTC, a potent inhibitor or NF-kappaB, decreases IL-1beta induced increase of NO production and NO synthase mRNA expression in insulin producing cells. No connection to diabetes type II is mentioned.

D7 teaches that generation of reactive oxygen species which induces the NF-kappaB pathway is implicated in development of insulin dependent diabetes mellitus. D7 suggests the use of antioxidants which prevent the activation of NF-kappaB pathway for preventing development of diabetes mellitus. Diabetes type II is not mentioned.

D8 teaches that PDTC inhibits IL-1beta-induced nitrite formation by human islets of Langerhans. No connection of this mechanism to type II diabetes is mentioned.

Inventiveness

Claims 6, 13

The subject-matter of claims 6, 13 is considered to lack an inventive step under Article 33(1) and (3) PCT for the following reasons:

The problem to be solved by the present application is to provide a medicament for treating or preventing diabetes type II.

The solution proposed by the present claims 6, 13 is the use of PDTC.

The solution known from D5 is the use of compounds inhibiting the activation of NF-kappaB. D5 explicitly teaches that it is because the claimed compounds can inhibit the activation of NF-kappaB, they are useful as preventive and therapeutic agents for diseases caused by the activation of NF-kappaB such as diabetes type II.

The solution proposed by claims 6,13 differs over that known from D5 in that PDTC is used rather than the NF-kappaB inhibiting compounds of D5. Consequently, the problem to be solved can be re-formulated as to provide NF-kappaB inhibitors for the treatment or prevention of diabetes type II alternative to those disclosed in D5. The ability of PDTC to inhibit activation of NF-kappaB is known from D6. Taking into the consideration the teaching of D5 together with that of D6, it would have been obvious to a person skilled in the art to use PDTC for the treatment of diabetes type II.

Claims 1, 8

Subject-matter of independent claims 1, 8 is considered as lacking an inventive step under Art. 33(1) and (3) PCT for the following reasons:

The solution proposed by present claims 1 and 8 is the use of IL-1Ra. However, it is considered that the application does not sufficiently prove that the technical problem was actually solved.

The example on pages 14-21 shows the following effects:

- elevated glucose concentration induces IL-1beta production and release in human islets *in vitro*;
- glucose induced IL-1beta is produced by pancreatic beta cells;
- beta cells of hyperglycemic diabetes-prone *Psammomys obesus* express IL-1beta and show impaired insulin production; normalisation of blood glucose restores insulin production and prevents IL-1beta expression;
- IL-1beta mediates glucose-induced NF-kappaB activation, Fas expression and beta cell apoptosis; inhibitor of IL-1beta, IL-1Ra, prevents those effects of IL-1beta;
- IL-1Ra improves impaired beta cell function caused by IL-1beta mediated glucotoxicity.

At least some of the above effects of IL-1beta and IL-Ra are known form the prior art:
- beta cell apoptosis and impaired beta cell function by IL-1beta and inhibition of those effects by IL-1Ra is known from D1 and D2
- the fact that high glucose level causes death of beta cells of *Psammomys obesus* which may contribute to the insulin deficiency is known from D4.

The animal and clinical studies described on pages 21-28 represent only suggested study regimens and do not provide any relevant results.

The example disclosed on pages 28-36 shows to following effects:

- IL-1Ra is expressed by human pancreatic beta cells and downregulated in type II diabetic patients;
- leptin decreases beta cell production of IL-1Ra and induces IL-1beta release in human islets *in vitro*;
- endogenously produced IL-1Ra is a survival factor of beta cells and preserves beta cell function in vitro (decrease of endogenous IL-1Ra protein expression

causes apoptosis of beta cells, this effect is prevented by addition of exogenous IL-1Ra);

- leptin induces beta cell apoptosis and impairs beta cell function *in vitro*; this effect is prevented by IL-1Ra.

The claimed solution is based only on the conclusion that taking into the consideration the above effects, the IL-1Ra might be useful for the treatment or prevention of diabetes type II. However, no direct connection between the described effects and the treatment or prevention of diabetes type II can be seen. No direct and unambiguous proof that IL-1Ra is actually effective in the prevention and/or treatment of diabetes type II is provided. As the technical problem was not shown to be solved, no inventiveness can be acknowledged.

Industrial applicability

Subject-matter of independent claims 1, 6 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of the present claims 8, 13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.